

CLINICAL RESEARCH ARTICLE

Conventional deep pressure algometry is not suitable for clinical assessment of nociception in painless diabetic neuropathy

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Background: In diabetic persons with painless neuropathic foot ulceration, foot skin was found to be insensate to noxious pinprick stimulation (stimulation area less than 0.05 mm²), while compression of deep subcutaneous foot tissues by Algometer II® (stimulation area 1 cm²) could evoke a deep dull aching. To elucidate this discrepancy, the Algometer II stimulation technique was critically reviewed by varying probe sizes and anatomical sites in the same study population 3 years later.

Methods: Ten control subjects without neuropathy and 11 persons with painless diabetic neuropathy (PLDN, seven of whom with diabetic foot syndrome, i.e., past painless foot ulcer, or inactive Charcot arthropathy) were re-examined using Algometer II. Deep pressure pain perception threshold (DPPPT) was measured in random sequence with stimulation areas of 0.5 cm², 1 cm², and 2 cm² (separated by 5 min intervals), at the plantar forefoot, the instep, and the hindfoot of both legs.

Results: In the control and PLDN groups, median DPPPTs differed significantly between stimulation areas (highest with 0.5 cm², intermediate with 1 cm², lowest with 2 cm²; $p < 0.001$), and varied moderately by anatomical site. Between-group differences were relatively small. Results of the 1 cm² assessments repeated 3 years apart were similar.

Conclusions: Algometer II readings represent spatial summation of low-threshold pressure-receptor rather than of high-threshold nociceptor stimulation and are, thus, unhelpful for assessing PLDN. Reproducibility of the measurements is good.

Keywords: *diabetic neuropathy; nociception; algometry; diabetes mellitus*

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In previous studies of feet with painless diabetic neuropathy (PLDN) (1–5), the authors have encountered unexplained discrepancies between deep pressure pain perception thresholds (DPPPTs) which were partly normal and cutaneous ‘pinprick’ pressure pain perception thresholds (CPPPTs) which were always extremely elevated (due to degeneration of intraepidermal nociceptors).

Blunt deep tissue pressure pain stimulation is part of established protocols of quantitative sensory testing (QST (6–8)). DPPPT or pressure pain tolerance threshold has long been measured using a pressure algometer (7, 8). Conventional pressure algometers are hand-held devices furnished with a mechanical or electronic force gauge and a plunger, which can be supplied with circular flat blunt rubber tips of various surface areas (e.g. 0.5 cm², 1 cm², 2 cm²) (Fig. 1). The operator presses the plunger perpendicularly to skin and underlying tissues with a steadily

increasing force. For a DPPPT to be determined, the study subject has to report when his/her pressure sensation turns to pain.

Blunt indentation of skin and subdermal tissues, whereby touch, pressure, and pain modalities are co-stimulated simultaneously, evokes deep tissue pressure pain or discomfort. The physical properties of the indented tissues, namely the compliance, affect the performance of the algometer. The pain quality evoked by an algometer with 1 cm² stimulation area is described as dull or aching (intolerable pressure discomfort). Pain intensity at reaching DPPPT is rated around 3/10 on visual analogue scale by healthy subjects (9).

Other types of pressure algometry stimulate by an inflatable cuff for compressing a limb over a contact area of approximately 400 cm² (9–11), or by two branches of forceps-like devices for squeezing a portion of skin and subcutaneous tissue (with stimulation areas on both



Fig. 1. Picture of the deep tissue pressure algometer with electronic force gauge (Algometer II®, SB-Medic, Sweden) used in the study.

branches (12, 13) or on one branch only (14)). However, these different stimulators will produce different DPPPTs within one person and at the same anatomical region due to different area sizes being stimulated, ranging from 1.5 N/cm² (with 400 cm² pressure area) to 60 N/cm² (with 1 cm² pressure area) and to 300 N/cm² (with 3 mm² pressure area) (15). Stimulation area-related DPPPT is caused by spatial summation, which is the augmented perception of the central nervous system (CNS) through collective input from a multitude of simultaneously stimulated receptors. As a result, the pain perception threshold in the CNS decreases, and the perceived pain intensity increases.

Spatial summation associated with conventional pressure algometry as described above (16–18) is well known. In healthy humans, spatial summation of pressure discomfort or pain perception (mediated by low-threshold mechanoreceptors at the endings of A-beta fibres) is of greater magnitude than that of sharp or burning pain (mediated by high-threshold mechanoreceptors at the endings of A-delta and C-fibres) (19). Both types of receptors, mechanoreceptors as well as nociceptors, may be co-stimulated by conventional pressure algometry (20, 21). In persons with PLDN, loss of deep tissue nociceptors had been anticipated, and the findings of DPPPTs in the normal range seemed inconsistent (1–5, 22). To examine whether anatomical sites of the foot, or the effects of spatial summation, would play a role, the impact of the stimulation area on algometer performance was studied at different sites of the feet in subjects with and without PLDN.

Materials and methods

Study design

A prospective observational clinical study was performed. Deep pressure pain was measured with the Algometer II

device, a clinically established method of QST (6–8, 13, 14, 16–18), approved by the local ethics commission. Written informed consent was obtained from every participant.

Participants

Healthy persons ($n = 10$) and persons with PLDN ($n = 11$), whose pressure pain perception had already been studied in our institution in 2011, were re-examined. Their former findings were published in this journal and elsewhere (1–5, 22). In particular, the PLDN-persons' CPPPTs measured by pinprick-stimulators at a plantar skinfold of the foot were unmeasurably elevated. Subjects with bleeding disorders; capillary fragility; mental disorders; cancer; rheumatic arthritis; foot ischaemia from peripheral artery disease; fever; hypoglycaemia; neuropathic pains; allodynia; multiple sclerosis; concurrent administration of anticoagulant, analgesic, antidepressant, or antiepileptic drugs were excluded, as were patients with an active ulcer or foot inflammation from infection or from active Charcot arthropathy grade 0 or 1 (23). Of the 11 persons with PLDN, seven had inactive diabetic foot syndrome (DFS, see Definitions section).

Definitions

PLDN was defined according to common clinical practice by a vibration perception threshold $< 5/8$ at the first metatarsophalangeal joint, measured with the graded Rydel–Seiffer tuning fork in subjects with established type-1 or type-2 diabetes mellitus, in whom neuropathic pains were absent. DFS was defined as past painless foot ulcer, or inactive Charcot foot grade 0 or grade 1 (23). DPPPT was defined as minimum force of pressure that produces pain or discomfort.

Measurements

For measuring DPPPT, a hand-held electronic pressure algometer with a strain pressure gauge (Algometer II, Sbmecic Electronics, Solna, Sweden) was used, see Fig. 1. The device has a digital readout of ramp rate and peak pressure force (in kPa), and holds peak pressure until reset. Three measurements were subsequently taken at three different locations of each foot, requiring almost 40 min to complete. The algometer probe was furnished with a stimulation area of 0.5 cm², 1 cm², or 2 cm². Each area size was randomly applied – with intermissions of 5 min – at the instep, a MTP joint, and below the medial ankle. The largest stimulation area was tried first, and the smallest area last, with the study persons being blinded to the area sizes. According to the manufacturer's instructions, the recording scale of the algometer was adapted to the stimulation surface by operating a switch on the meter. The probe was pressed perpendicularly on the skin over the targeted structures, so as to increase indentation steadily by a rate of approximately 50 kPa per second. Care was taken not to place the probe on callosities.

The subjects were lying on a hospital bed for assessing DPPPT. They were asked to keep their eyes closed during the measurements and to report the onset of pressure discomfort, or pressure pain, whereupon the stimulation was stopped. In particular, they were asked to respond verbally as soon as they felt that the – steadily increased – algometer pressure became painful or uncomfortable ('the moment of transition between strong and painful pressure'(9)), to describe their perceptions at reaching DPPPT (either 'dull and soaring' or 'sharp and stinging'), and to rate pain intensity on a 10-point numerical rating scale (NRS).

Diabetic blood glucose concentrations (except for hypoglycaemia) were not accounted for, as they had no influence on pain measurements in previous studies. The maximum force to stimulate DPPPT was limited to 1,400 kPa (= 140 N/cm² ~ 14 kg) as in our previous studies, in order not to overstress hypoaesthetic/anaesthetic tissues in patients with painless neuropathy.

Anatomic regions exposed to stimulation

Hindfoot

The area below the medial malleolus was chosen to target the deltoid ligament. The following anatomical structures and tissues were exposed to the algometer pressure probe: glabrous skin, subcutaneous fat tissue; medial plantar vein, artery and nerve; the tendons and tendon sheaths of mm.tibialis posterior, flexor digitorum longus, and flexor hallucis longus; the tibialis posterior artery; and the fascia (retinaculum musculorum flexorum). Previous studies with 1 cm² pressure area had reported that healthy subjects' DPPPT averages around 40 to 90 N/cm² over lateral foot ligaments (anterior talofibular ligament, calcaneofibular ligament) (24–26).

Midfoot

The instep was chosen to target the abductor hallucis muscle. The following structures were co-stimulated: glabrous skin and subdermal fat tissue, plantar fascia; medial plantar vein artery and nerve. Previous studies had reported that healthy subjects' 1 cm² DPPPT averages around 20 to 50 N/cm² over abductor hallucis muscle (1, 4, 5, 27, 28).

Forefoot

The second or third MTP joint was chosen as target and was stimulated from the plantar side. Thereby, the following anatomical structures and tissues were co-compressed: glabrous skin; subdermal fat tissue; superficial and deep transverse ligaments; plantar aponeurosis; tendons and tendon sheaths of the flexor digitorum brevis muscle; common plantar digital arteries, veins, and nerves; and joint capsule. Previous studies had reported that healthy subjects' DPPPT over MTP joints averages around 40 to 70 N/cm² (1, 22, 27, 28).

Data analyses

Forces are presented as N/cm² (1 N/cm² = 10 kPa ~ 0.1 kg). Measurements from both feet were averaged for further analysis, as previous studies had shown no differences between both feet, neither in healthy nor in diabetic subjects. In order not to lose values exceeding the safety range (140 N/cm²), a constant of 1 was added (giving 141 N/cm²) prior to analysis. Data were displayed as median (range), unless stated otherwise. Friedman analysis of variance and 3 × 3 factorial ANOVA for independent samples was applied for descriptive purposes, as appropriate. A two-sided Bonferroni-corrected $p < 0.0125$ was considered significant.

Results

Demographic data of the participants are summarised in Table 1, showing that the PLDN and control study groups were not quite homogeneous. Median DPPPTs were in the healthy range at each of the sites under study (MTP joint, foot instep, below the medial malleolus) in the PLDN group ($p > 0.0125$), and tended to be higher over the MTP joint than over the foot instep and below the medial malleolus ($p > 0.0125$) in both groups. In PLDN patients, DPPPTs exceeded the safety limit of 140 N/cm² with a stimulation area of 0.5 cm² in seven measurements, with a stimulation area of 1 cm² in four measurements, and with a stimulation area of 2 cm² in two measurements, compared with one measurement (with 0.5 cm² stimulation area) in the control persons. In both PLDN and control groups, median DPPPTs were lowest with 2 cm² stimulation area, intermediate with 1 cm² stimulation area, and highest when 0.5 cm² stimulation area was applied ($p < 0.0002$), see Table 2 and Fig. 2. There was no interaction between measurement site and stimulation area in controls (ANOVA: $p = 0.24$) and PLDN patients (ANOVA: $p = 0.77$). Pain intensity at reaching DPPPT was similar in the control and PLDN group (NRS 3.75 (2–7) controls versus 4 (0–5.5) PLDN).

Table 1. Demographic data of subjects under study

Subjects	Controls	PLDN
Numbers	10	11
Males/females, <i>n</i>	5/5	7/4
Height, cm	174 (158–186)	179 (169–188)
Weight, kg	72 (54–90)	89 (62–107)
Body mass index, kg/m ²	24 (19–29)	28 (19–35)
Age, years	51 (37–67)	64 (54–82)
Diabetes mellitus type 1/2, <i>n</i>	n.a.	8/3
Diabetes mellitus duration, years	n.a.	37 (10–49)
Current Haemoglobin A1c, %	n.a.	7.9 (6.7–8.5)

Numbers, or medians (range). n.a. = not applicable; PLDN = painless diabetic neuropathy.

Table 2. Deep pressure pain perception thresholds (DPPPTs) attained with different stimulation areas

		Algometer pressure area			Friedman test <i>p</i>
		0.5 cm ² DPPPT, N/cm ²	1 cm ² DPPPT, N/cm ²	2 cm ² DPPPT, N/cm ²	
Controls, <i>n</i> = 10	MTP joint	88 (59–141)	68 (23–90)	36 (17–57)	<i>p</i> < 0.0001
	Instep	49 (41–119)	39 (25–58)	23 (16–30)	<i>p</i> < 0.0001
	Medial malleolus	67 (29–99)	40 (29–53)	25 (19–32)	<i>p</i> < 0.0001
PLDN, <i>n</i> = 11	MTP joint	123 (47–141)*	89 (33–141)*	52 (30–141)*	<i>p</i> = 0.0002
	Instep	73 (36–141)*	52 (26–141)*	27 (20–141)*	<i>p</i> = 0.0006
	Medial malleolus	70 (46–141)*	37 (29–141)*	27 (17–57)*	<i>p</i> = 0.0002
	Friedman test	* <i>p</i> = 0.0136	* <i>p</i> = 0.0346	* <i>p</i> = 0.0136	

Medians (range).

The smallest algometer stimulation area evoked pain that was more of a ‘stinging’ nature in the control (*n* = 5) rather than the PLDN (*n* = 3) group, while the largest

stimulation area in both groups evoked ‘dull pressure discomfort’ only. Adverse effects of the measurements like bruising were not evident.

At MTP joint, 1 cm² DPPPTs measured 3 years before were not different (n.s., data not shown). Since the first DPPPT study, of the PLDN patients, one sustained a Charcot arthropathy grade 1 and one patient had a relapse of a healed Charcot foot; seven patients had relapse of healed feet ulcer (duration of follow-up: 3 years on average).

Discussion

The present data corroborate our previous preliminary findings that conventional algometer pressure stimulation evokes deep pain or discomfort at relatively low force per area even in patients with PLDN, whose foot skin is completely insensitive to any noxious impact. When compared with pinprick stimulation which aims to activate single cutaneous nociceptors (i.e. intraepidermal nerve endings of A-delta or C-fibres), deep pressure stimulation by conventional algometer technique inevitably stimulates low-threshold pressure receptors in subepidermal tissues (Merkel’s disks, Meissner’s corpuscles, Pacinian corpuscles, feeding A-beta fibres), and probably together with nociceptors. Spatial summation of low-threshold pressure-receptor activation induces a pain percept like ‘dull pressure discomfort’, which differs markedly from ‘stinging or burning’ evoked by pinprick stimulation of cutaneous high-threshold nociceptors. In cases of PLDN, where the endings of A-delta and C-fibres degenerate and eventually vanish before the A-beta fibres are affected (22), DPPPT at the foot stimulated by conventional pressure algometry may be normal although the foot skin proves to be insensate to painful pressure stimuli (although not necessarily to touch with the palm of a hand; *EAC*, unpublished observation). This finding is consistent with human experiments applying skin anaesthesia (29–32). Lidocaine blockade of cutaneous nociceptors, increasing mechanical pain thresholds, but not tactile detection thresholds (32), changes

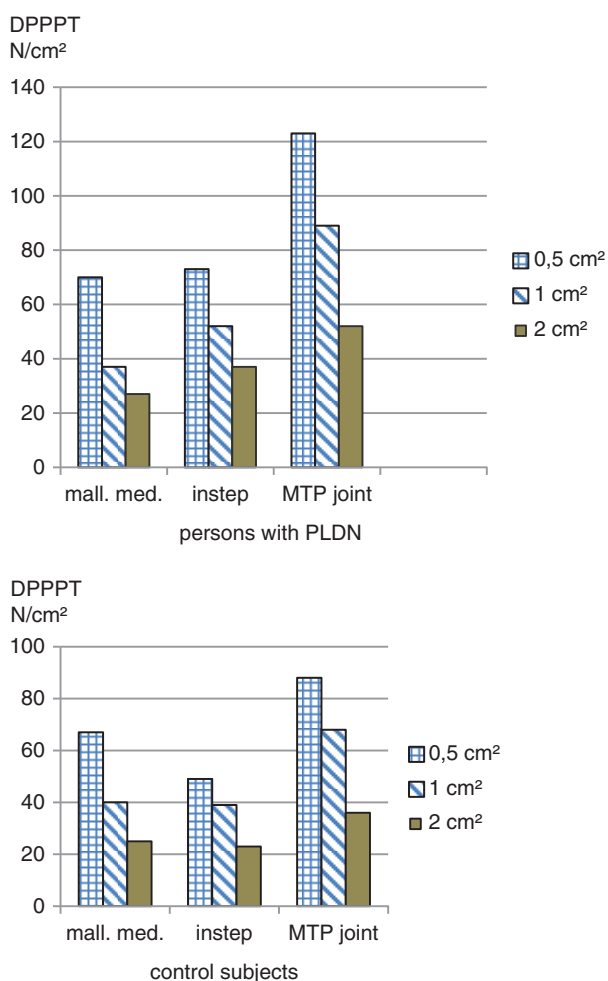


Fig. 2. DPPPTs (N/cm², medians) attained with various stimulation area sizes. DPPPT = deep pressure pain perception threshold, MTP = metatarsophalangeal, mall. med. = medial malleolus, PLDN = painless diabetic neuropathy.

the character of mechanically stimulated pain from sharp pricking pain to dull pressure discomfort (15). Interestingly, the mechanoreceptors stimulated by conventional algometer are subject to sensitisation from inflammation due to a single strong trauma (4), or chronic repetitive submaximal trauma (33, 34), since DPPPT and mechanical detection threshold decrease in response to these conditions in healthy subjects.

The lack of a measurable deterioration of DPPPT over 3 years on average corroborates the data by Gibbons et al. (35) who showed no changes in heat pain, cold pain, and vibration perception thresholds at the foot in diabetic patients with and without neuropathy over a period of 3 years.

Study limitations

Unequivocally, the study has limitations due to the small sample size precluding potential statistical differences to become significant. Due to lack of pre-existing data on the effect of stimulation area size in PLDN, a power-calculation before planning the study was not feasible. Other weaknesses of the study relate to this method of quantitative pain sensitivity testing as such, which is only semi-objective and prone to biases. And last, but not least, pain in deep tissues (visceral pain) is not normally evoked by stimuli evoking somatic pain-like thermal and mechanical energies.

Conclusion

In conclusion, spatial summation of a multitude of low-threshold pressure receptors simultaneously activated by innocuous force during conventional pressure algometry explains the seeming discrepancy between absence of pinprick-perception and presence of deep pressure pain perception in persons with PLDN and painless foot ulcers. Our previous hypothesis is, thus, unlikely that 'residual C-fibre nociceptors inside musculoskeletal structures may contribute to deep dull aching' (3) as stimulated by Algometer II in feet with PLDN. Conventional deep pressure algometry is unsuitable for assessing nociceptive dysfunction at the diabetic foot. Other methods seem more promising in this respect, for example, quantitative pinprick stimulation or intraepidermal electrical stimulation (36, 37).

Conflict of interest and funding

The author has no conflict of interest to declare and has not received any funding of his work.

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